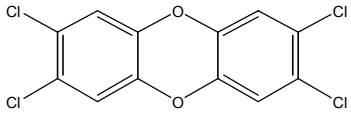
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD); DIOXIN*

CAS No. 1746-01-6

First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD or TCDD) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.5, 1977; NTP 201, 1982; NTP 209, 1982; IARC S.4, 1982; IARC S.7, 1987). When administered by gavage, TCDD increased the incidences of thyroid follicular cell adenomas in male rats and neoplastic nodules of the liver in female rats. When administered by the same route, TCDD increased the incidences of hepatocellular carcinomas in mice of both sexes and thyroid follicular cell adenomas in female mice. When administered in the diet, the compound induced hepatocellular carcinomas and squamous cell carcinomas of the lung and hard palate nasal turbinates in female rats. It also induced squamous cell carcinomas of the tongue and hard palate nasal turbinates in male rats (Kociba et al., 1978a; idem., 1978b). When administered topically, TCDD induced fibrosarcomas of the integumentary system of female mice. When administered by intraperitoneal injection, TCDD induced thymic lymphomas and liver tumors in infant mice. In a two-stage skin carcinogenesis study, TCDD was a weak tumor initiator in mice when applied topically before application of 12-*O*-tetradecanoylphorbol-13-acetate. TCDD was also effective as a promoter, increasing the incidences of hepatocellular carcinomas in rats treated subcutaneously with TCDD and intragastrically with N-nitrosodiethylamine.

An IARC Working Group reported that there are no adequate data to evaluate the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in humans (IARC S.7, 1987). There are no reports of human exposure to TCDD alone. However, there are numerous case-control studies associating soft tissue sarcoma and lymphoma with exposure to phenoxyacetic acids or chlorophenols, probably contaminated with TCDD. A number of cohort studies revealed an increased incidence of deaths from cancer including lymphoma and soft tissue sarcoma when exposed to TCDD during the manufacture or use of 2,4,5-trichlorophenol and/or 2,4,5-trichlorophenoxy acids. Several epidemiology studies of humans exposed to herbicides contaminated with TCDD indicate an association between exposure and stomach cancer, lymphoma, and soft tissue sarcoma (IARC S.4, 1982; ATSDR, 1989f).

PROPERTIES

TCDD has a physical state of colorless to white needles. It is almost insoluble in water, slightly soluble in *n*-octanol, methanol, and lard oil, and soluble in organic solvents (dichlorobenzene, chlorobenzene, benzene, chloroform, acetone). TCDD is stable in water, DMSO, 95% ethanol, or acetone. It can undergo a slow photochemical and bacterial degradation

---

* This substance has been proposed for upgrade to the *known to be a human carcinogen* category. The proposed listing is currently in litigation. Depending on the outcome of the litigation an addendum may be published following the Court's ruling.

but is normally extremely stable. TCDD, however, is degraded when heated in excess of 500 ^{o}C or when exposed to ultraviolet radiation under specific conditions. Photodecomposition does not occur in aqueous solution (HSDB, 1997; Lewis, 1996; Radian, 1991).

TCDD is an inadvertent contaminant in herbicide precursors and, thus, in the herbicides themselves (Schecter et al., 1997b; IARC V.69, 1997). Since TCDD is a by-product of the manufacture of polychlorinated phenols, it has been detected in commercial samples of 2,4,5-trichlorophenol (2,4,5-TCP) and was found in the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Before 1965, commercial 2,4,5-T contained up to 30 ppm TCDD or more. By the mid-1980s, however, commercial 2,4,5-T contained no more than 0.01 ppm TCDD. Since 1971, regulatory agencies in a number of countries worldwide enforced a maximum of 0.1 ppm TCDD in 2,4,5-T. Agent Orange (a 50:50 mixture of the *N*-butyl esters of 2,4,5-T and 2,4-D that was used in the Vietnam War as a defoliant during 1962-1970) contained 2 to 30 ppm TCDD. It has also been detected in the herbicide 2-(2,4,5-trichlorophenoxy)propionic acid (Silvex), and may be present in *o*-chlorophenol, 1,2,4,5-tetrachlorobenzene, Ronnel (fenchlorphos), and 2,4-D (OHMTADS, 1985).

USE

TCDD has no known commercial applications but is used as a research chemical.

PRODUCTION

TCDD is currently not produced commercially in the United States, but it is synthesized on a laboratory scale. It is not imported into the United States (OHEA, 1985).

Polychlorinated dibenzo-*p*-dioxins (PCDDs) (including TCDD) are also produced by paper and pulp bleaching (Silkworth and Brown, 1996); by incineration of municipal, toxic, and hospital wastes; PCB-filled electrical transformer fires; and smelters (Schecter, 1994). Because it is a by-product of 2,4,5-TCP production, TCDD is also found as a contaminant in some phenoxy herbicides such as 2,4,5-T, in some pesticides such as chlorinated phenols, and in wood preservatives such as pentachlorophenol (Schecter, 1994; IARC V.69, 1997).

EXPOSURE

PCDDs as well as their structural analogs and usual co-contaminants (the polychlorinated dibenzofurans [PCDFs]) are widespread environmental contaminants. They bioaccumulate throughout the food chain because of their lipophilic character and slow metabolism *in vivo* (De Jongh et al., 1995). The primary source of TCDD exposure to humans is from food. In adults in the United States, average totals of TCDD toxic equivalents are approximately 1 to 6 pg/kg/day (Schecter et al., 1994a, 1994b). This leads to an average blood TCDD equivalent level between 20 and 40 ppt on a lipid basis (Schecter, 1994). More than 90% of the dioxins found in humans in the general population are due to consumption of meat including poultry, dairy products, and fish (Schecter et al., 1994a, 1994b, 1997a).

Historically, chlorinated dibenzo-*p*-dioxins (CDDs), including TCDD, have been deposited onto soil through pesticide applications and disposal of CDD-contaminated industrial wastes, and via land application of paper mill sludges. Currently, however, atmospheric fall-out

of CDD-laden particulates and gases appears to be the most predominant source of CDDs to soil. Evidence indicates that TCDD is resistant to natural degradation (ATSDR, 1997-H011).

REGULATIONS

EPA regulates TCDD under the Clean Water Act (CWA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Resource Conservation and Recovery Act (RCRA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Toxic Substances Control Act (TSCA) as a hazardous waste and toxic pollutant. A reportable quantity of 1 lb (0.454 kg) has been established for TCDD. The maximum contaminant level for the chemical in community water systems and non-transient, non-community water systems is 3×10^{-8} mg/L. FDA regulates TCDD in beverages, specifically bottled water; the allowable concentration is also 3×10^{-8} mg/L. NIOSH has recommended that the exposure limit of TCDD be the lowest feasible concentration. OSHA regulates TCDD under the Hazard Communication Standard and as a hazardous chemical in laboratories. Regulations are summarized in Volume II, Table B-136.